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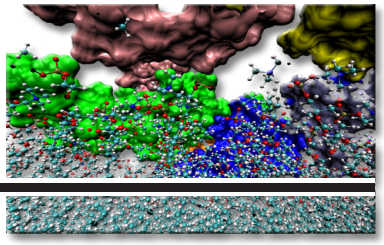

Research Findings on the Blue Gene Offer Insight into Molecular Basis of Parkinson's Disease

Familial studies of Parkinson's disease suggest that its progression is associated with defects that cause increased aggregation of the protein known as alpha-synuclein (aS). Researchers from the San Diego Supercomputer Center combined high-end computation with biochemical and electrophysiological experiments to model the molecular basis for aggregation and test hypotheses generated by their simulations using electron microscopy and various biochemical techniques. Their findings will improve the understanding of the molecular basis of the disease and its treatment.

A research team from the San Diego Supercomputer Center (SDSC) at University of California–San Diego (UCSD) recently proposed and elucidated the molecular mechanism of the progression of Parkinson's disease. Using molecular modeling and molecular dynamics simulations in combination with biochemical and ultrastructural analysis, the team showed that increased aggregation of a protein known as alpha-synuclein (aS) can lead to the formation of harmful pore-like structures in human membranes (Figure 1). In contrast, beta-synuclein (bS) appeared to block the propagation of alpha-synucleins into the structures.

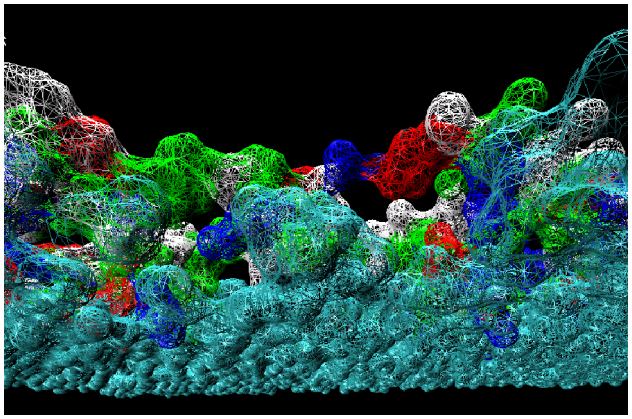

Figure 1. A membrane (cyan, cut from the bottom) embedded with the residues of alpha-synuclein pentamer (cut at the top on the level of the highest membrane atom).

The team's findings provide insights into the molecular mechanism for Parkinson's disease progression and have broad applicability to other diseases. They also provide a test bed for identifying possible therapeutic interventions through computational modeling. These insights will help focus the search for treatment, based on an improved understanding of the molecular mechanisms of the disease's progression. The test bed offers a computational framework for generating hypotheses about treatments that can be adapted readily to state-of-the-art, high-throughput virtual screening of pharmacophores as potential lead compounds. Academic and pharmaceutical companies could use such a modeling system for further testing and improving potential pharmacophores and other palliative therapies.

Allocations of processor-hours from the Department of Energy's (DOE) INCITE program enabled the SDSC team to perform complex calculations for the research on high-performance Blue Gene/L computers at the Argonne Leadership Computing Facility. The team also used a Blue Gene/L system at SDSC.

The researchers conducted a comprehensive investigation of aS penetration into the membrane, including a thorough study of pore creation. They employed a computational approach that used the NAMD molecular dynamics package, along with the MAPAS program and a set of docking programs on the Blue Gene/L computer system. Together, the programs enabled the team to make predictions for conformational changes of proteins, explore protein-protein interactions and/or aggregation, and study interaction of proteins individually or as a complex with the membrane.

The larger simulations focused on the interaction of higher-level aS oligomers with the membrane, which increases the number of atoms in the system up to approximately 800,000. Given the encouraging correlation between the molecular dynamics modeling predictions and laboratory experimental results, the team expects to make steady progress with the computational model for Parkinson's disease progression and develop cues for design of effective drugs based on computational modeling and simulations.

The computational work conducted in this research also has significant benefits in driving the creation of new simulation capabilities. The work requires the researchers to adapt existing tools for molecular simulation to the new Blue Gene architecture. The architecture is unique in providing a very large and dense processor array, using relatively less memory per computational node. As a result, the strategies for running simulations on this platform require the adaptation of existing community codes to a new computing paradigm. For example, the community code CHARMM requires the full list of data objects to be resident on each node, a strategy that might not work well on the Blue Gene. Efforts are under way at SDSC, IBM, and elsewhere to adapt codes like this to petascale platforms.

The Argonne Leadership Computing Facility and the INCITE program directly support the primary mission of DOE's Office of Advanced Scientific Computing Research to discover, develop, and deploy computational and networking tools that enable researchers in the scientific disciplines to analyze, model, simulate, and predict complex phenomena.

Contributors:

Igor Tsigelny
San Diego Supercomputer Center, UC San Diego

Mark Miller
San Diego Supercomputer Center, UC San Diego

Eliezer Masliah
UC San Diego

For more information on this subject, please contact:

Igor Tsigelny
San Diego Supercomputer Center
University of California–San Diego
858-822-0953
itsigeln@ucsd.edu

For more information about ALCF, please contact:

Pete Beckman, Acting Division Director
Argonne Leadership Computing Facility
Argonne National Laboratory
630-252-9020
beckman@mcs.anl.gov

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